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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/599,980	04/03/2007	Roland Reiner	067802-5008	7700

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EXAMINER	
KRISHNAN, GANAPATHY	
ART UNIT	PAPER NUMBER
1623	
MAIL DATE	DELIVERY MODE
03/11/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/599,980	REINER ET AL.	
	Examiner	Art Unit	
	Ganapathy Krishnan	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 February 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *23 and 27-49* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *23 and 27-49* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

A Request for Continued Examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed 2/13/2009 has been entered.

The Request for Continued Examination filed 2/13/2009 has been carefully considered. The following information provided in the amendment affects the instant application:

1. Claims 1-22 and 24-26 have been canceled.

2. Claim 23 has been amended.

3. Remarks drawn to rejections under 35 USC 103(a).

Claims 23 and 27-49 are pending in the case.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.

2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 23 and 27-49 are rejected under 35 U.S.C. 103(a) as being unpatentable over Marler et al (Plast. Reconstr. Surg., 2000, 105, 2049-2058; document cited in International Search Report of 10/16/2006), in view of Bent et al (Neurourology and Urodynamics, 2001, 20, 157-165; document cited in International Search Report of 10/16/2006), Agerup (US 5,633,001; document cited in International Search Report of 10/16/2006), Vanderhoff et al (WO 96/39464; document cited in International Search Report of 10/16/2006), The Merck Index (12th Edition, 1996, page 758, entry # 4465) and Hawley's Chemical Dictionary (1997, page 1092), all of record.

Marler et al teach tissue augmentation (increasing shape and volume) via subcutaneous injection of a composition comprising an alginate, into a rat (page 2049 Abstract, first, second and last paragraphs; page 2050, right column, first full paragraph). The composition comprised of 1% medium viscosity alginate and a medium viscosity alginate covalently bonded to RGD-a cell adhesion peptide. The alginates were used in cell culture medium to provide nutrients and

phosphate buffered saline (page 2050, right col., last paragraph). The alginate was reconstituted as a 2% solution and gelled via crosslinking with calcium ions (page 2051, left col., first full paragraph). The alginate solutions with or without the cells were allowed to gel in vivo, after injection of a mixture of alginate, cell and calcium ions (page 2051, right column, first paragraph).

Bent et al teach the treatment of incontinence by injection of alginate solution crosslinked (gelled) with calcium ions and containing chrondrocytes, into the sphincter muscle (page 157, abstract through page 158, middle).

However, Marler et al and Bent et al do not teach the molecular weight of the alginate and the use of microparticles of alginate crosslinked with barium even though the use of alginate microparticles are disclosed including injection into muscle tissue.

Agerup, drawn to method of tissue augmentation, teaches enlargement of tissue (same as increasing volume) like esophagus, various sphincters, urether and rectum via injection of a composition comprising a carrier gel, which could be alginate (0.05-50%) in combination with tissue augmenting substance, which could be a carbohydrate polymer (col. 1, lines 5-16; col. 2, lines 45-59). The composition can additionally contain therapeutically active substances like growth factors, hormones, vaccines, cytokines, antivirals, bactericidal compounds and other pharmacologically active compounds (col. 2, line 65 through col. 3, line 8). Example 2 teaches the use of alginate as a carrier gel, which is made harder (i.e, gelled by crosslinking) with calcium ions (col. 3, lines 54-61). Even though Agerup uses alginate as a carrier, one of skill in the art will recognize, based on the teaching of Marler that alginate itself could be used for augmentation either alone or in combination with other agents.

Vanderhoff et al teach polymer particles of about 150 micrometers for use in soft tissue augmentation (page 4, line 20 through page 5, line 4). The injectable particles can also contain encapsulated drugs and medications (page 5, lines 5-9; lines 25-31; page 7, lines 6-35). The water soluble polymers can be polysaccharides (page 8, lines 32-34). One of the desirable polymers is sodium alginate, since it is biocompatible, biodegradable, and non immunogenic and in the form of microspheres is a good candidate as carrier of drugs (page 9, lines 7-20). Several types of crosslinking agents can also be used depending upon the polymer used and can be readily determined by one of skill in the art (page 9, lines 21-35). For crosslinking of the microparticles, pH can be adjusted to adjust the rate of crosslinking (page 10, lines 20-21). Even though Vanderhoff's teaching is drawn to a process for producing microparticles, he suggests the use of such particles also for tissue augmentation. One of skill in the art will use such microparticles of alginate for tissue augmentation as taught by Marler, Bent and Agerup.

The Merck Index and Hawley's both teach that gluconolactone and EDTA are complexing (sequestering) agents.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use alginates, crosslinked and uncrosslinked, in the form of microspheres, for increasing the volume of tissue in a subject, as instantly claimed since the use of such is taught using analogous alginates for the same purpose.

One of skill in the art would be motivated to use alginates in the method as instantly claimed since Marler teaches that the use of alginates offers additional advantages like chemical modification to induce desirable properties, is readily available and has been approved by FDA for use in human patients (Marler, page 2054, right column, first and second paragraphs).

According to Vanderhoff, one of the desirable polymers is sodium alginate, since it is biocompatible, biodegradable, and non immunogenic and in the form of microspheres is a good candidate as carrier of drugs (page 9, lines 7-20). With so many advantages, one of skill in the art would prefer to use alginate over other polymers suggested in the prior art.

One of skill in the art would also prefer to use EDTA or gluconolactone since both are taught to be sequestering agents. The use of citrate is also logical since it is a component of the well known citrate buffer used for adjusting pH. In line with the teaching of Vanderhoff regarding the adjustment of pH for adjusting the rate of crosslinking, the use of the biocompatible citrate is preferable (Vanderhoff page 10, lines 20-21). It is well within the skill level of the artisan to adjust the percentages of the agents, the size of the microparticle and the molecular weight of the alginate in order to obtain maximum beneficial effects.

Response to Applicants' Arguments

Applicants have traversed the 103(a) rejection of record in the Final Action arguing that:

1. None of the references teach or suggest the use of alginate with the specific molecular weight as instantly recited. The Examiner has not established that molecular weight of the alginate used in the cited art methods is recognized as a result-effective variable. Applicants have identified the molecular weight of the alginate is a parameter for increasing long term stability. The cited art do not provide alginates with molecular weight more than 100 kDa.

2. The state of the art at the time of filing (Mancini et al) explored in vivo characteristics including stability and focused primarily on mannuron/guluron ratio and ignores the

relevance of molecular weight of the alginate. Hence the cited art could provide motivation to optimize only the mannuron/guluron ratio in an attempt to increase long term stability.

3. Vanderhoff teaches that ionic bonds formed by crosslinking with calcium ions may be broken down by change in external environmental conditions, e.g. chelating agents. The preferred crosslinking is via the use of agents that crosslink via covalent bonds. This is a teaching away from the instant invention. Vanderhoff cannot possibly be using ionic linkers since the molecular weight of the alginate material is much lower that the alginate presently claimed. The ionic bonding mentioned by Vanderhoff would not be applicable for crosslinking of high molecular weight alginates. Vanderhoff must use additional covalent crosslinking to confer even minimum stability. Vanderhoff's covalent crosslinkers are toxic and does not allow for in situ crosslinking. Covalently crosslinked polysaccharides are degraded in vivo, which leads to smaller crosslinked fragments, which in turn evokes side effects. The Examiner has not provided reasoning or basis as to how one would go about removing impurities in prior art compositions. This is not taught in the prior art.

3. Agerup is completely different from the subject matter currently claimed since it uses dextranomeric microbeads for tissue augmentation and also does not teach the use of high molecular weight alginate.

Applicants' arguments have been considered but are not found to be persuasive. The Mancini reference, which applicants have said has been appended to their Remarks, has actually

not been appended. Examiner's argument regarding the relevance of Mancini reference is based on Applicants description of Mancini's teaching.

The cited prior art may not have taught or suggested the use of high molecular weight alginate as recited in instant claim 23. But the cited art has not specifically mentioned any problems with stability if low molecular weight alginates are used or only alginates having molecular weights in the range recited in the instant claims are stable. One of ordinary skill in the art knows well that in polysaccharides molecular weight is also a variable parameter. Mancini may have explored the relevance of mannuron/guluron ratio with respect to stability. But unless Mancini has also explored the relevance of molecular weight and found it not contributing to stability one cannot conclusively say that molecular weight is not a result affecting variable. Crosslinking with covalent crosslinkers and ionic crosslinkers like calcium ions can be performed with alginates having a range of molecular weights including the low molecular weight alginates. There is no teaching or suggestion in the prior art of record that this cannot be done. Even though Vanderhoff teaches that ionic bonds formed by crosslinking with calcium ions may be broken down by change in external environmental conditions, e.g. chelating agents and preferred crosslinking is via the use of agents that crosslink via covalent bonds one ordinary skill in the art will recognize that this is with respect to only the use of calcium ions. For long term stability one can use other ions like sodium or potassium. Vanderhoff does not disclose any problems using these.

Applicants have argued that the Examiner has not provided reasoning or basis as to how one would go about removing impurities in prior art compositions since this is not taught in the prior art. Vanderhoff teaches separation and purification of crosslinked particles via filtration

after which they can be washed and dehydrated with methanol (page 12, line 29 through page 13, line 5). This step will remove impurities. One of ordinary skill in the art also knows well that other suitable solvents can be used in the washing step and also the washing step can be repeated till the particles are free of impurities.

Agerup exemplifies a similar invention with dextranomer. His invention is still relevant to the instant invention since it deals with ionically crosslinked polymeric materials for tissue augmentation.

According to Applicants, alginates having molecular weights as instantly claimed have higher stability compared to the ones disclosed in the prior art. In the instant Specification (page 9, lines 10-11), applicants have disclosed that alginates having average molecular weights of from 20kDa to 10,000kDa can be used. The instant Example (at page 14 of the Specification) teaches the preparation of an alginate solution that is used for making the crosslinked product but does not disclose the molecular weight of the alginate. There are no comparative results that show that the alginates having the molecular weight range as instantly claimed are superior in stability compared to the ones disclosed in the prior art either.

Conclusion

Claims 23 and 27-49 are rejected

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ganapathy Krishnan whose telephone number is 571-272-0654. The examiner can normally be reached on 8.30am-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia A. Jiang can be reached on 571-272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Ganapathy Krishnan/
Examiner, Art Unit 1623

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Supervisory Patent Examiner, Art Unit 1623